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ORIGINAL ARTICLE

Efficacy and safety of six hourly vaginal misoprostol versus intracervical dinoprostone: a randomized controlled trial

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Abstract
Objective To compare the efficacy and safety of intravaginal misoprostol versus dinoprostone cervical gel for cervical ripening and labour induction.
Methods We carried out an experimental clinical trial in which we enrolled 130 cervical consecutive patients with cervical ripening, randomly assigned to one of the following two treatment groups: (1) intravaginal misoprostol and (2) intracervical dinoprostone gel. A total of 50 μm of misoprostol was placed in the posterior vaginal fornix every 6 h for a maximum period of 24 h and 0.5 mg of dinoprostone was administrated in the uterine cervix every 6 h, for a maximum period of 24 h. The primary outcome measure was the number (rate) of women who went to vaginally deliver within 24 h of the protocol initiation.
Results Among 130 patients evaluated, 65 were allocated to the misoprostol group and 65 to the dinoprostone group. The proportion of vaginal delivery within 24 h was significantly higher in the misoprostol group (75%) than in the dinoprostone group (53.8%) (RR = 1.40, 95% CI [1.07–1.45], $P = 0.02$). There was no significant difference between the mean time interval of delivery in the misoprostol group and the dinoprostone group (14.9 vs.15.8 h) ($P = 0.51$). The Bishop score was significantly higher in the misoprostol group, 6 h after the onset of the study (1.38; relative risk, 95% CI [1.02–1.85], $P = 0.03$). The Caesarean delivery rate for fetal distress was higher in the dinoprostone group (21 vs. 10.8%, $P = 0.15$). The tachysystole (Misoprostol 6.1% vs. dinoprostone 4.6%, relative risk 1.15, 95% CI [0.6–2.24]) and hyperstimulation syndrome rates (Misoprostol 7.6% vs. dinoprostone 4.6%, relative risk 1.26, 95% CI [0.72–2.24]) were slightly increased in the misoprostol group than in the dinoprostone group without reaching the level of statistical signification.
Conclusion Misoprostol as used in this protocol is more effective than cervical dinoprostone gel application in the cervical ripening and labour induction. There is a tendency for an increase in the rate of tachysystole and hyperstimulation syndrome.

Keywords Misoprostol · Dinoprostone · Cervical ripening · Labour induction

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Introduction

Cervical ripening is a current practice in obstetrics [1]. In this respect, several techniques have been used such as Foley catheters and laminar's [2]. Dinoprostone has been widely effective for cervical ripening and labour induction, and it is currently the only pharmacologically approved molecule for this purpose. Although it is expensive and requires refrigeration for storage, many patients require oxytocin augmentation after dinoprostone administration [2]. A vaginal application of misoprostol has been reported in over 9,000 women worldwide and seems to have a safety profile similar to endocervical and intravaginal dinoprostone [3]. However, concern arises about the use of higher doses of

misoprostol administered vaginally (50 mcg and more), which is associated with uterine contractile abnormalities such as tachysystole and hyperstimulation syndrome. Accordingly, the use of low dose misoprostol regimen has been recommended by the American College Of Obstetricians and Gynaecologists [4]. Several trials were conducted to find out a safer and effective regimen; yet, only some of them have shown the effectiveness and safety of the protocol using a 50-mcg vaginal dose of misoprostol [5–7]. Hence, to date, debates still continue about optimal dose, dose regimen and route of administration.

In this randomized trial, we investigate whether the six hourly administration of 50-mcg vaginal dosing of misoprostol is safe and efficient for cervical ripening and labour induction, compared to intracervical dinoprostone gel application, which is assessed by the rate of vaginal delivery within 24 h.

Materials and methods

The study of population included a subgroup of women, who attended the University Hospital Medical Centre for medically-indicated labour induction between the 1 August 2003 and 30 April 2004. A randomized controlled trial was carried out to test the null following hypothesis: "there is no significant difference in efficacy of 50 mcg vaginally administered misoprostol every 6 h and 0.5 mg intracervical dinoprostone gel for inducing labor and cervical ripening at term".

The criteria for enrolment include the following:

1. Obstetric indications for labour inductions include hypertensive disorders of pregnancy, isoimmunisation, post-dates and fetal growth restriction.
2. Medical complications, including diabetes and renal diseases associated with pregnancy.
3. The absence of active labour or fetal distress.
4. No previous caesarean section delivery or other type of uterine surgery.
5. Singleton pregnancy with vertex presentation and no contra-indication to vaginal delivery.

All women presenting the following were excluded from the study:

1. Less than 18 years old.
2. Gestational age less than 36 weeks.
3. Premature rupture of membranes.
4. History of dystocic or forceps delivery.
5. History of more than one episode of surgical interruption of pregnancy.
6. Multiparity (more than four).
7. Estimated fetal weight more than 4,200 g.

Women who met the study's criteria were invited to participate voluntarily, and those who gave a written informed consent were enrolled. The protocol had previously been submitted to the local ethical committee and was approved; no medical laboratories had sponsored this study. First, the bishop score was assessed before the administration of the study drug. Subjects were assigned to misoprostol or dinoprostone groups by using a computer generated randomization table. A table of group allocation was predetermined once a subject was enrolled in the study and the physician responsible for the study was advised. Women allocated to the misoprostol group were administered 50 mcg (one quarter of 200 mcg tablet) of misoprostol (Cytotec®, Pharmacia, UK) intravaginally in the posterior fornix. The dose was repeated every 6 h until a favourable bishop score was achieved (at least six), the maximum dose of misoprostol was 200 mcg, or four, quarter tablets. Patients in the active phase of labour (cervical dilatation of at least 4 cm) with arrest of dilatation (no changes in cervical dilatation for two more hours) received oxytocin for augmentation. Women randomized to the dinoprostone group were administered 0.5 mg of dinoprostone gel (Prepidil)® that provides 0.5 mg of dinoprostone. This dose was repeated every 6 h until a favourable bishop score was achieved (at least six) for a maximum dose of 2 mg (four cervical gel applications). Cervical ripening and fetal heart monitoring were assessed before and an hour after the cervical ripening. Once the 6-h ripening interval period for misoprostol or dinoprostone was completed, uterine activity was re-evaluated. According to the medical centre, induction protocol subjects with a favourable bishop score were induced with oxytocin. As soon as the cervical dilatation permitted, artificial rupture of membranes was performed. Meanwhile, labour continuous tocography and fetal heart rate monitoring were performed to detect any signs of hyperstimulation or fetal distress. The recognition of episodes of hyperstimulation was managed with left maternal repositioning, removing the tablet, oxygen therapy via nasal catheter and an intra muscular anti-spasmodic agent injection (Phloroglucinol, Spasfon®).

The primary outcome measure was the number (rate) of women who went to vaginally deliver within 24 h of the initiation of the protocol. Other outcome variables including the induction to delivery interval, the oxytocin requirements, method of delivery and the uterine hyperstimulation failed induction rates and neonatal outcomes. Baseline recorded data were maternal

age, parity, gestational age, indication for the induction and the induction cervical score. Physicians managing labour were not blinded to study group allocation; labour induction was considered successful if the participant delivered within 24 h of initiation of the protocol. After delivery, we reviewed the uterine contraction pattern of each fetal heart rate monitoring to assess the frequency of Tachsystole and hyperstimulation syndrome. Tachsystole was defined as at least six contractions in 10 min for two consecutive 10-min periods. Hyperstimulation syndrome was defined as the presence of tachysystole associated with fetal tachycardia, late decelerations and/or loss of variability. Trial sample size was calculated on the primary outcome of the rate of vaginal delivery within 24 h. Assuming that 50% in the control group would deliver within 24 h of the induction, and taking a 20–25% increase in this rate in the treatment group as clinically significant, we estimated that a sample size of 62 women per group was identified ($\alpha = 0.05$, $\beta = 0.20$). Statistical analysis was performed with "SPSS 11.0" statistical software. Entry characteristics and outcome variables were analysed with the student test, χ^2 analyses or Fischer's exact test. Through all analysis, $P < 0.05$ was considered statistically significant.

Results

Among the 250 women who presented labour induction during the study period, 120 (52%) were ineligible, 59 had a bishop score more than or equal to 6, 25 patients had a previous caesarean section or other uterine surgery, 7 had fetal distress and 29 met other exclusion criteria. A total of 130 women, who met inclusion criteria consented to participate and were enrolled in the study (Fig. 1). The distribution of patient age, parity, gestational age, weight and bishop score were similar in the two groups (Table 1). Indications for labour induction were similar in the misoprostol and dinoprostone groups (Table 2). There were no significant differences in maternal demographics and indications for labour induction in the two groups. The proportion of vaginal delivery within 24 h was significantly higher in the misoprostol group (75%) than in the dinoprostone group (53.8%) (RR = 1.40, 95% CI [1.07–1.45], $P = 0.02$). All patients in the misoprostol group reached the active phase labour. After the first 6-h period of the cervical ripening, 44 patients (67.7%) of the misoprostol group and 32 (49.2%) in the dinoprostone group had a favourable bishop score (RR = 1.38, 95% CI [1.02–1.85], $P = 0.03$) (Table 3). The mean interval to delivery was shorter in the misoprostol group (14.9 vs. 15.8 h) ($P = 0.51$) than in the dinoprostone group without reaching the level of statistical signification. The mean delay from initiating the protocol to the active phase was similar in the two groups (12.86 vs. 13 h) ($P = 0.68$).

A significantly higher percentage of patients who were treated with misoprostol (86.1%, 56/65 women) achieved active labour. The mean active phase duration was slightly shorter in the misoprostol group (97.6 min) than in the dinoprostone group (113.4 min) ($P = 0.62$). The maternal side effects associated with

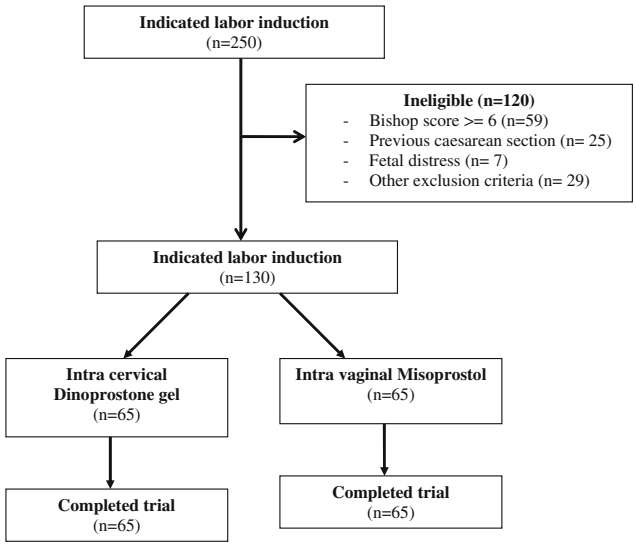

Fig. 1 Trial profile

Table 1 Demographic characteristics of the sample study

Demographic	Misoprostol group ($n = 65$)	Dinoprostone group ($n = 65$)	P value
Maternal age (year)[a]	27.2 ± 4.6	29.9 ± 5.4	0.81
Body mass index (Kg/m²)[a]	30.7 ± 5.5	31.9 ± 5.9	0.23
Gestational age (days)[a]	279.6 ± 12.6	279 ± 12.3	0.56
Initial Bishop score[a]	2.1 ± 1.2	2.3 ± 1.29	0.25
Parity[a]	1.8 ± 0.9	1.9 ± 1.2	0.33
Primiparous (n/N)	31/65	30/65	0.86

[a] Data are given as mean ± Standard deviation

Table 2 Indications for labor induction in the groups

Indication for induction	Misoprostol group ($n = 65$) (%)	Dinoprostone group ($n = 65$) (%)	P value
Postterm	33 (50.8)	32 (49.2)	0.86
Hypertensive disorders	15 (23.1)	18 (27.7)	0.54
Diabetes mellitus	2 (3)	5 (7.7)	0.24
IUGR[a]	10 (15.4)	5 (7.7)	0.17
Oligohydramnios	5 (7.7)	5 (7.7)	1

[a] Intrauterin growth restriction

Table 3 Intrapartum variables

Intra partum variables	Misoprostol ($n = 65$) (%)	Dinoprostone ($n = 65$) (%)	RR [95% CI] P value
Mean of Initial bishop score[a]	2.1 ± 1.2	2.3 ± 1.29	0.25
Favourable bishop score after 6 h (>5)	44 (67.7)	32 (49.2)	1.38 [1.02–1.85] 0.03
Time to delivery interval (h)[a]	14.9 ± 6.9	15.8 ± 9.7	0.51
Delay to the active phase (h)[a]	12.86 ± 6.9	13 ± 9.3	0.68
Vaginal delivery within 24 h	49 (75)	35 (53.8)	1.40 [1.07–1.45] 0.02
Need for oxytocin	9 (13.8)	21 (33.9)	0.43 [0.21–0.86] 0.02
Number of doses[a]	1.2 ± 0.5	1.3 ± 0.6	0.5

[a] Data are given as mean ± Standard deviation

prostaglandin use including nausea, vomiting, fever and diarrhoea were noted in 12 patients of the misoprostol group (18.4%) and 16 patients of the dinoprostone group. Table 4 compares the frequency of side effects in each group. The rate of hyperstimulation syndrome was higher in the misoprostol group (7.6%) than in the dinoprostone group (4.6%) ($P = 0.47$) (RR = 1.27, 95% CI [0.72–2.24]). Tachysystole syndrome was observed more frequently in the misoprostol group (6.1%) than in the dinoprostone group (4.6%) (RR = 1.15, 95% CI [0.69–2.24], $P = 0.69$) (Table 4).

There was no difference in fetal weight, 3.187 and 3.211 kg respectively, in the misoprostol and the dinoprostone groups ($P = 0.15$). The mean Apgar score at first and in the fifth minute was not different in the two groups; Table 4 shows the detailed Apgar score and the need for a transfer in a neonatal intensive care unit in each group.

We noted a significantly higher caesarean section rate in the dinoprostone group (32.3 vs. 15.4%) ($P = 0.02$). There were, however, no significant differences in the caesarean rate about fetal distress between the two groups (10.8 vs. 21%, $P = 0.15$), respectively, in the misoprostol and the dinoprostone group. The rate of abnormal fetal heart rate (FHR) pattern during labor was similar in the two groups (29.2%). Tachycardia was more frequent in the misoprostol group (9.2%) than in the dinoprostone group (1.5%) ($P = 0.05$) (Table 5). No significant difference was noted between the two groups regarding the type of fetal heart rate (FHR) patterns and the rate of meconium passage (Table 5).

Discussion

This current study confirms the efficacy of 6-h, 50 mcg misoprostol for cervical ripening compared to intracervical dinoprostone gel. Several studies and a Cochrane pregnancy and child birth group [4, 5, 7] have

Table 4 Intrapartum complications and neonatal parameters

Complication, mode of delivery and neonatal outcomes	Misoprostol ($n = 65$) (%)	Dinoprostone ($n = 65$) (%)	RR [$CI_{95\%}$] P value
Tachysystole	4 (6.1)	3 (4.6)	1.15 [0.69–2.24] 0.69
Uterine Hyperstimulation	5 (7.6)	3 (4.6)	1.27 [0.72–2.24] 0.47
Mode of delivery			
Vaginal	51 (78.4)	41 (63)	1.72 [1–2.95] 0.02
Forceps	4 (6.2)	3 (4.6)	
Caesarean	10 (15.4)	21 (32.3)	0.58 [0.34–0.99] 0.02
Apgar score <7			
1st minute	2 (3.1)	6 (8.1)	0.48 [0.14–1.63] 0.13
5th minute	0 (0)	3 (4)	−0.12
Transfer in intensive care unit	4 (6.1)	6 (9.7)	0.79 [0.36–1.72] 0.51

Table 5 Fetal heart rate pattern and meconium passage in the two groups

Fetal Heart rate pattern–meconium passage	Misoprostol ($n = 65$) (%)	Dinoprostone ($n = 65$) (%)	RR [$CI_{95\%}$]
Normal	45 (69.2)	43 (66.1)	1.07 [0.74–1.57] 0.7
Type I	6 (9.2)	5 (7.7)	1.10 [0.62–1.94] 0.75
Type II	7 (10.7)	11 (16.9)	0.75 [0.41–1.38] 0.31
Bradycardia (FHR < 120 b/m)	–	2 (3)	0.98 [0.42–1.49] 0.62
Tachycardia (FHR > 160 b/m))	6 (9.2)	1 (1.5)	1.79 [1.25–2.55] 0.05
Meconium passage	12(18.4)	16(24.6)	0.82 [0.52–1.32] 0.39

FHR Fetal heart rate

confirmed that vaginal misoprostol (25–100 mcg) was more effective than oxytocin or dinoprostone at usual recommended doses for labour induction. Misoprostol can achieve a higher rate of vaginal delivery interval within 24 h and significantly lower caesarean section rates than in the dinoprostone group, but with increased rates of uterine hyper stimulation or fetal heart rate changes. As the efficacy of misoprostol became certain, debate continues, as to the optimal dosing regimen of vaginally misoprostol. In general, lower doses compared to higher doses were associated with more need for oxytocin augmentation (dose < 50 mcg), less uterine hyperstimulation, with or without fetal heart rate changes and a non-significant trend to fewer admissions to neonatal intensive care unit [1]. Based on these results, Hofmeyr et al. [1] recommended a starting dose of 25 mcg every 4 h. Sanchez-Ramos et al. [6] compared between 25 and 50-mcg intravaginal misoprostol for cervical ripening and labour induction and they found that a higher dose was associated with a shorter interval to vaginal delivery, higher rate of deliveries within 24 h and less frequent need for oxytocin augmentation, but it was unclear whether it is as safe as the 25 mcg doses. Our results are consistent with these studies. More interesting is the decreased rates of tachysystole and hyper stimulation syndrome in our study; these rates are less than those in the protocol using 50 μg every 4 h [5, 8] and seem to be equivalent to those observed with the dose of 25 μg every 4 h [8] with more efficacy. This supposes that when the dose of 50 μg is used, the 6-h interval or more could be safer.

To reduce the risk of side effects, some authors have decreased the dose of the drug [9], or prolong the interval [10]. In a recent randomized controlled trial, Papanicoulaou et al. [11] have compared 50 mcg vaginal misoprostol every 9 h with vaginal dinoprostone. In this study, misoprostol have been found to be more effective than vaginal dinoprostone. They achieved a low rate of uterine hyperstimulation syndrome. However, these rates were twofold higher in the misoprostol group (2.5% with misoprostol and 1.2% with dinoprostone). Another recent randomized controlled study consisted of using 6-h, 50-mcg regimen [12] and found a decreased rate of hyperstimulation and tachysystole. Our findings, in accordance with the previous Cochrane metaanalysis [3], showed a high rate of fetal tachycardia and staining amniotic liquid. In contrast, we observed a slight increase in the rates of tachysystole and hyperstimulation syndrome in the misoprostol group.

Lyons et al. [13] have recently shown that in term pregnant rats, a higher dose of misoprostol is needed to induce prostaglandin E2 (PGE2) secretion in the cervix than in the myometrium, and that prostaglandin E2 receptors (EP3) are differentially expressed in the myometrium (increased) than in the cervix (unaltered) in response to misoprostol. These findings indicate that misoprostol acts better on the myometrium than on the cervix, but an even higher dose is needed in order to ripen the cervix. Thus, it seems reasonable that increasing the interval between repeated misoprostol doses should reduce the risk of an asynchrony between a well or even hyper-stimulated uterus and a still not efficiently ripened cervix [11]. The rate of vaginal delivery within 24 h in our study was 75%; it was similar to those of Ghidini et al. using 50 mcg at 4-h interval with less rates of tachysystole and hyperstimulation syndrome. Hence, based on the preceding results [10–12] and our own, we suppose that dose of misoprostol seems to be more correlated to the efficacy; however, the interval seems to be correlated with rates of tachysystole and hyperstimulation syndrome. This suggestion needs further precise pharmacokinetic studies in order to be confirmed.

Some authors suggested that dose of misoprostol should be adapted to the indication of labour induction; Rosenberg et al. [14] published a randomized trial, in which they compared 50-mcg intravaginal misoprostol to 2 mg of dinoprostone. They conclude that vaginal misoprostol at this dose should be reserved for non-fetal indication for cervical ripening and that indications to labour induction, where fetal condition could be compromised, dose of misoprostol should be decreased to 25 mcg. Therefore, the best scheme of administration of misoprostol has still to be established. A rigid scheme should probably not be used because the individual response to misoprostol can be variable; some authors suggested a vaginal pH role [15].

Sublingual administration seems to be promising for cervical ripening. Indeed, recently published pharmacokinetic study revealed that when compared with oral and vaginal routes, sublingual misoprostol achieved its peak serum concentration in an interval similar to that achieved by the oral route [16]. Absorption and bioavailability of misoprostol thus seems to be enhanced by the sublingual route. However, in a recent published randomized trial, 100 mcg of sublingual misoprostol was found more effective than 50 mcg but was associated with a higher incidence of tachysystole and uterine hyperstimulation syndrome [17]. Thus, the best scheme of administration for sublingual route is not well established. Benefits from the sublingual route might include less frequent need for vaginal examinations, greater freedom of position in the labour bed and ease of administration [17].

Some authors reported cases of uterine rupture during induction of labour with misoprostol [18]; therefore, its use should be reserved to hospitals equipped with adequate fetal supervision, as emphasized by the American College of Obstetricians and Gynaecologists Bulletin [19]. Our results are consistent with those of the literature regarding the safety and efficacy of this protocol but they contain some bias: (1) the higher caesarean delivery rate observed in the dinoprostone group may be explained by the high frequency of oligohydramnios in this group. (2) Physicians who were responsible for intrapartum management were not blinded to study group allocation and therefore differential intrapartum management including decision with regard to the timing of amniotomy or use of oxytocin augmentation could have biased our results.

Conclusion

Our results confirm to those of some studies, using the 6-h, 50-mcg intravaginal misoprostol for cervical ripening and the labour induction at term. The 6-h interval seems to be safe, though our study is limited in size; further randomized studies should be conducted comparing different doses and intervals of misoprostol to determine the most effective and safe regimen and the factors affecting the response to misoprostol. These studies could establish protocols adapted to the indication of labour induction.

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